Gene Expression and Structural Skeletal Responses to Long-Duration Simulated Microgravity in Rats. Victoria E. Rael[1,2], Yasaman Shirazi-Fard[3,4], Candice Tahimic[3,4], and Ruth K. Globus[4]. [1]Space Life Sciences Training Program (SLSTP), NASA Ames Research Center, [2]Biological Sciences Collegiate Division, University of Chicago, Chicago, IL, [3]Wyle Laboratories, [4]Space Biosciences Division, NASA Ames Research Center.

Spaceflight has deleterious effects on skeletal structure and function, specifically causing profound loss in bone mass, density, and strength, as well as changes in expression levels of genes related to oxidative stress [Hyeon et al., Smith et al.]. It is known that bone resorption remains elevated after spaceflight and that bone density and strength fail to recover completely even years following spaceflight [Smith et al., Carpenter et al.]. However, our current understanding of the signaling pathways and molecular mechanisms that control bone loss and that link oxidative stress, bone resorption, and mechanical unloading of skeletal tissue is incomplete. Here, we aim to examine skeletal responses to simulated long-duration spaceflight on bone loss using the ground-based hindlimb unloading (HU) model in adult (9 months old) male rats. We hypothesized that simulated microgravity leads to the temporal regulation of oxidative-defense genes and pro-osteoclastogenic factors, showing progression and eventual plateau during long-term unloading, and that transient changes at early timepoints in these pathways precede skeletal adaptations to long-duration unloading. We will identify oxidative stress and bone resorption-related changes using global gene expression analysis (Affymetrix arrays) for both acute (within 14 days) and long-term timepoints (90 days). We will also use quantitative PCR to examine changes in expression of genes related to oxidative metabolism (e.g. Nrf2, SOD-1), bone turnover (resorption and formation markers, e.g. TRAP, osteocalcin respectively, SOST), and osteoclastogenesis (e.g. RANKL, OPG) at both early and late timepoints. We will then use detailed microarchitectural and structural analysis through microcomputed tomography to relate gene expression changes with structural changes in bone, expecting that plateaus in gene expression correlate with long-term changes in bone microarchitecture.

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